REMARKS

Upon entry of this Amendment, claims 64-83 will be pending in the present application. Claims 65-72 have been amended to provide proper antecedent basis by replacing "A" with "The". Such amendments do not go to issues of substantive patentability. New claims 73-83 have been added. The amendments are fully supported by the specification and no new matter has been added.

Applicant notes with appreciation the Examiner's acknowledgment of the novelty and nonobviousness of the present invention in view of the prior art of record. Office Action at 17.

I. THERE IS NO OBVIOUSNESS-TYPE DOUBLE PATENTING.

Claim 71 stands rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claim 1 of U.S. Patent No. 5,023,243. Applicant traverses.

In determining whether a nonstatutory basis exists for a double patenting rejection, the issue is whether any claim in the application defines an invention that is merely an obvious variation of an invention claimed in the patent. When the claimed subject matter is patentably distinct from the subject matter claimed in a commonly owned patent, a double patenting rejection is improper. *Eli Lilly & Co. v. Barr Labs.*, Inc., 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). Any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. § 103 obviousness determination (*In re Braat*, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991)); however, a double patenting rejection must rely on a comparison of only the claims. MPEP § 804, part III.

Claim 71 recites a method for selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids, the method comprising the steps of synthesizing a stabilized oligonucleotide having a sequence substantially complementary to a subsequence of a messenger ribonucleic acid coding for the target protein, introducing the stabilized oligonucleotide into the cell, and hybridizing the stabilized oligonucleotide to the subsequence of messenger ribonucleic acid to inhibit

expression of the target protein, wherein the oligonucleotide is stabilized to inhibit degradation by nucleases.

In contrast, claim 1 of U.S. Patent No. 5,023,243 recites a method of selectively inhibiting *in vivo* synthesis of one or more specific targeted proteins comprising the steps of synthesizing an oligodeoxyribonucleotide having a nucleotide sequence substantially complementary to at least a portion of the base sequence of messenger ribonucleic acid coding for the targeted protein. In the claims of the '243 patent, at least a portion of the oligodeoxyribonucleotide is in the form of a phosphotriester to limit degradation *in vivo*. Claim 1 of the '243 patent calls for introducing the oligonucleotide into the cell and hybridizing the oligonucleotide to the subsequence of messenger ribonucleic acid to substantially block translation of the base sequence and to inhibit synthesis of the targeted protein. Claim 1 of the '243 patent does not render obvious claim 71 of the present application. No *prima facie* case of nonstatutory obviousness-type double patenting exists.

Applicant requests reconsideration and withdrawal of the rejection.

II. THE CLAIMS ARE ENABLED BY THE SPECIFICATION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH.

A. Prosecution to Date

The present case was filed June 16, 1993 and has a priority date of October 23, 1981. In prosecution, Applicant has submitted at least three formal responses, four declarations, an appeal brief, a reply to the Examiner's answer, and numerous references, addressing the enablement issue and showing that the same should be withdrawn. This amendment again addresses all of the Examiner's contentions. If the Examiner elects to maintain this rejection, he is respectfully requested to provide the factual support required by 37 C.F.R. § 1.104 (d).

B. State of the Art in 1981

The state of the art at the time of filing of the parent application is evidenced by, *inter alia*, peer-reviewed scientific references, statements in the present application, and

the declarations of Dr. Ruth, Dr. Schwartz, and Dr. Crooke filed to date. The peer-reviewed scientific references include at least eleven pre-priority date references, such as Miller et al. (Biochemistry, 13(24): 4887-4906 (1974) (describing the stabilized alkylphosphotriester DNA analogs described in the application)); Befort et al. (Chem.-Biol. Interactions, 9:181-185 (1974) (reporting that ribonucleic acids stabilized by methylation are taken up by cells and exhibit anti-viral activity)); Miller et al. (Biochem. 20(7): 1874-1880 (1981) (reporting a stabilized alkyl phosphonate DNA analog having activity *in vitro*); Harvey et al. (Biochem. 12(2):208-214 (1973) ("Harvey") (describing 5'-terminal alkyl phosphorothioate groups as protecting groups in oligonucleotide synthesis)); Malkievicz et al. (Czech. Chem. Commun., 38:2953-2961 (1973) ("Malkievicz") (demonstrating the use of alkyl thioyl moieties as blocking groups in oligonucleotide synthesis)); and Summerton et al. (J. Theor. Biol. 78:77-99 (1979) ("Summerton") (evidencing that pre-priority date references describing modified oligonucleotides were well known to one of ordinary skill in the art prior to Applicant's effective filing date). All of these have been provided heretofore. U.S. Patent No. 3,687,808 to Merigan et al. (describing stabilized phosphorothioate oligonucleotides available as early as 1972), Matzura and Eckstein (Eur. J. Biochem., 3: 448-452 (1968) (describing the nuclease resistance of phosphorothioate oligonucleotides)), DeClercq et al. (Virology, 42:421-428 (1970) (describing the resistance of thiophosphate-substituted oligonucleotides to degradative enzymes)), Agarwal and Riftina (Nuc. Acids Res., 6:9, 3009-3024 (1979) (describing the synthesis of oligonucleotides containing methyl and phenylphosphonate linkages)), and Holý ("Synthesis and Biological Activity of Some Analogues of Nucleic Acids Components," in PHOSPHORUS CHEMISTRY DIRECTED TOWARDS BIOLOGY, W.J. Stec, Ed., Pergamon Press, 53-64, 1980 (describing modified nucleotide analogs having hydroxyl-containing aliphatic chains that are stable *in vivo* and display inhibitory and substrate activities)), submitted with the Supplemental Information Disclosure Statement filed herewith, further evidence the state of the art at the time of filing.

In view of the state of the art at the time of the 1981 filing and further in view of the guidance as to how to make and use the invention provided in the application, Applicant submits that the specification enables claims reciting methods of selectively

inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins by introducing an oligonucleotide that is substantially complementary to a subsequence of a messenger ribonucleic acid coding for the target protein into the cell and hybridizing the oligonucleotide to the subsequence of the target messenger ribonucleic acid to inhibit expression of the target protein.

Notwithstanding the foregoing, Applicant attaches hereto a Declaration of Dr. Stanley T. Crooke supporting the Applicant's arguments as presented herein. Dr. Crooke, an eminent authority in the field, declares that: (1) as of the priority date, one of ordinary skill in the art was aware of the existence of stabilized forms of oligonucleotides in addition to phosphotriesters and would have been guided by the disclosure of the application to the other stabilized oligonucleotides that are suitable, along with phosphotriester oligonucleotides, for *in vivo* use according to the claimed invention; (2) nothing more than routine experimentation is involved in determining which forms of stabilized oligonucleotides will work in the invention; (3) the stabilized oligonucleotides known in the art at the effective filing date are taken up by cells, are sufficiently stable to exert biological activity, and specifically hybridize to the target mRNA; and (4) the *in vitro* models correlate to *in vivo* biological activity of the stabilized oligonucleotides, as substantiated by pre- and post-filing references. Absent facts to the contrary, Dr. Crooke's statements must be accepted as true and the rejection withdrawn.

C. The Enablement Rejection

Claims 64-72 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicant acknowledges that a 35 U.S.C. § 101 rejection is neither pending nor at issue. The Examiner states that there are two separate issues which need to be addressed: "[T]he application [does not] adequately identif[y] stabilized oligonucleotides other than those that are phosphotriesters. . . [and] the instant application does not provide an enabling disclosure for the use of deoxyribonucleotides in vivo." Office Action at 3-4. Applicant respectfully disagrees.

The enablement requirement of 35 U.S.C. § 112, first paragraph, mandates that the specification teach those in the art how to make and use the claimed invention

without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). The test of enablement is not whether ***any*** experimentation is necessary, but whether, if experimentation is necessary, it is ***undue***. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Wands*, 8 U.S.P.Q.2d at 1404.

The factors to be considered in determining whether any necessary experimentation is undue include:

i. the breadth of the claims;
ii. the nature of the invention;
iii. the state of the prior art;
iv. the level of one of ordinary skill;
v. the level of predictability in the art;
vi. the amount of direction provided by the inventor;
vii. the existence of working examples; and
viii. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Id. (citing *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. & Int. 1986)). Any conclusion of nonenablement ***must*** be based on the evidence as a whole. *Id.* In order to make a rejection, the examiner has the burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). The burden then shifts to the applicant to provide persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973).

The Examiner has not established a *prima facie* case of nonenablement. One having ordinary skill in the art would be able to make and use the claimed invention using the application as a guide. Therefore, the claims are enabled by the application. Applicant has previously submitted several declarations and attaches a further Declaration attesting to the enablement of the claims. Applicant also cites numerous references that support enablement. Based on the evidence as a whole, the claims are

enabled: one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation using the application as a guide.

D. The Instant Application Provides Guidance as to Which Oligonucleotides to Use.

Claim 71 of the present invention is directed to methods of selectively inhibiting expression of a target protein using a ***stabilized*** oligonucleotide that binds to a messenger ribonucleic acid (mRNA) encoding a target protein in order to selectively inhibit expression of the target protein.

The Examiner alleges that "the instant application does not teach one of skill in the art the full scope of the claimed invention in the sense that the application adequately identifies stabilized oligonucleotides other than those that are phosphotriesters." Office Action at 3. The Examiner further alleges a "lack of guidance as to which types of oligodeoxyribonucleotides to use in the invention or . . . potential candidate oligodeoxyribonucleotides to use" and a failure "to establish that one of skill in the art would readily know which oligodeoxyribonucleotide to use." *Id.* at 5. Thus, the first issue alleged by the Examiner is that the application fails to adequately identify forms of stabilized oligonucleotides in addition to phosphotriesters that may be used in the invention.

1. One important aspect of Applicant's invention is the selection of the oligonucleotide sequence to effect hybridization.

The Examiner has failed to focus on the inventive aspects of the invention. A point of novelty of the invention is not which form of stabilized oligonucleotides is used therein. Indeed, various forms of stabilized oligonucleotides were known in the art in 1981, as discussed below. One important inventive principle of Applicant's invention is ***the selection of the oligonucleotide sequence to effect hybridization*** to the messenger ribonucleic acid encoding the target protein. *See, e.g.,* Response submitted August 19, 1994 at 3-5 (explaining case law requiring an analysis under 35 U.S.C. § 112, first

paragraph to be confined to the patentable or "inventive principles" of the claimed methods[1]).

The Examiner asserts that the statement that "any nucleic acid will work" in the methods of the invention is in conflict with Applicant's earlier statement that "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect," and, therefore, that the inventive principle of the Applicant's invention is the form of stabilization of the oligonucleotide. Office Action at 6 (underlining in original). Applicant disagrees.

Applicant's statement regarding the Zamecnik reference indicates ***only that an unprotected oligonucleotide*** would be degraded ***more quickly*** *in vivo* than a protected oligonucleotide. An unprotected oligonucleotide would also work: it would enter the cell, bind to the target mRNA, and inhibit expression of the target protein encoded thereby. Applicant recognizes that an unprotected oligonucleotide would likely not achieve the ***level*** of inhibition of expression of the target protein achieved by a stabilized oligonucleotide, as a result of more rapid degradation. This, however, does not suggest that an unprotected oligonucleotide will not work in the invention. This explanation is supported by Example 1 of the specification:

> It is believed that transforming the oligonucleotide to a phosphotriester form will ***improve*** the oligonucleotide's stability in vivo due to ***enhanced resistance*** against various degradative enzymes. However, the oligonucleotide will eventually degrade because of spontaneous de-ethylation, which leaves the molecule unprotected. Indeed, by controlling the initial level of ethylation, the in vivo ***degradation rate*** can be controlled.

Specification at 18 (emphasis added; underlining in original). In other words, a difference between the stabilized and unstabilized oligonucleotides lies in the rate of their

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[1] *See, e.g., In re Lange*, 209 U.S.P.Q. 288 (C.C.P.A. 1981) (holding that "the disclosure in question must be read in light of the knowledge possessed by those skilled in the art, and that knowledge can be established by affidavits of fact composed by an expert.); Application of Herschler, 200 U.S.P.Q. 711 (C.C.P.A. 1979) ("[C]laims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. . . . [A] functional recitation of those known compounds in the specification may be sufficient as that description.") ; *In re Fuetterer*, 138 U.S.P.Q. 217 (C.C.P.A. 1963) (explaining that the invention was the claimed combination of an inorganic salt with other components, not the discovery that certain inorganic salts had the necessary properties for use in the invention, and holding that patent law does not require the applicant to discover which salts had such properties and would function properly in the invention).

degradation and the level of inhibition of expression of the target protein achieved, not in their ability to enter the cell, bind the target mRNA, and inhibit expression of the target protein. Both stabilized and unstabilized oligonucleotides will work in the invention.

The Examiner may not pick and choose among the features of the invention. Such is the exclusive province of the Applicant.

2. Applicant need not teach what is known in the art.

In response to Applicant's argument that the specification provides adequate guidance to those of ordinary skill in the art as to which oligonucleotides to use in the invention and the declarations submitted in support thereof, the Examiner argues "that the scant statements in the application . . . in regard to the use of stabilized forms of oligonucleotides are [not] adequate direction for those of skill in the art . . .. It is not enough to hint at what may be desirable, expecting those of skill in the art to perform the undue experimentation that is required to make the invention work." Office Action at 11.

Section 112 requires the specification to be enabling only to persons "skilled in the art to which it pertains, or with which it is most nearly connected." *DeGeorge v. Bernier*, 226 U.S.P.Q. 758 (Fed. Cir. 1985). Thus, a patent need not teach, and preferably omits, what is known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Paperless Accounting, Inc. v. Bay Area Rapid Transit System*, 231 U.S.P.Q. 649 (Fed. Cir. 1986) ("A patent applicant need not include in the specification that which is already known to and available to the public."); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). A person of skilled in the art is deemed to possess not only basic knowledge of the particular art, but also "the knowledge of where to search out information" for section 112 purposes. *In re Howarth*, 210 U.S.P.Q. 689 (C.C.P.A. 1981). Furthermore,

> [w]ell known text books in English are obvious research materials. Similarly, public records concerning U.S. patents are likely to be checked. . . . Thus, U.S. patents are considered pertinent evidence of what is likely to be known by persons of ordinary skill in the art . . . . When an applicant seeks to add necessary information to a specification by incorporating a source for the information by reference, public accessibility of that source alone may be the controlling factor. On the other hand, when no guide at all has been given, as here, an applicant must

> show that anyone skilled in the art would have actually possessed the requisite knowledge or would reasonably be expected to check the source which the applicant relies upon to complete his disclosure and would be able to locate the information with no more than reasonable diligence.

Id. at 692-93 (citations omitted). Thus, contrary to the Examiner's assertion that those of skill in the art are not expected to conduct literature searches, *Howarth* sets forth the controlling standard under 35 U.S.C. § 112 that one of skill in the art ***is*** expected to check "obvious research materials" to determine what is known in the art for enablement purposes. If the Examiner disagrees with this standard, Applicant requests that the Examiner cite the support upon which he relies. 37 C.F.R. § 1.104(d)(2).

Like U.S. patents and English textbooks, scientific journals are "obvious research materials" and pertinent evidence of the knowledge of one of ordinary skill in the art. One of ordinary skill in the art would reasonably be expected to check scientific journals for information regarding stabilized oligonucleotides, particularly in view of the statements contained in the specification. Nowhere in the specification are the methods of the invention limited to phosphotriester-stabilized oligonucleotides. In fact, throughout the entirety of the specification, it is clearly stated that phosphotriester oligonucleotides are simply a ***representative example*** of the stabilized oligonucleotides that may be used in the methods of the invention. For example, the specification states at page 3, "[i]n a presently ***preferred embodiment*** of the invention, by way of example and not necessarily by way of limitation, a stabilized oligonucleotide, ***preferably*** in a phosphotriester form, is provided . . . " and at page 4, "[t]he ***preferred oligonucleotide*** . . . for increased stability, may be transformed to a more stable form, ***such as*** a phosphotriester form, to inhibit degradation during use." The application again states at page 5 that the oligonucleotide "can be transformed to a more stable form, ***such as*** a phosphotriester form, to inhibit degradation. . . ." Example I clearly demonstrates that stabilized forms of oligonucleotides for use in the invention may be found in scientific journals, as *exemplified* by the stabilized, nuclease resistant phosphotriester form of an oligonucleotide taught by Miller et al. (Biochemistry, 16:1988 (1977) ("Miller 1977")). Given the language of the specification including "such as," "preferred," and variations thereof, one of ordinary skill in the art would readily understand that other forms of

stabilized oligonucleotides were contemplated and equally useful in the methods of the invention. One of ordinary skill in the art would thus reasonably be expected to check scientific journals for other forms of stabilized oligonucleotides to use in the methods of the invention. Nothing more than reasonable diligence would be required to locate such information. According to the standard set forth in *Howarth*, satisfying this expectation does ***not*** constitute undue experimentation. In fact, those of ordinary skill in the art are expected to stay current with current technology, especially by reading scientific journals.

Applicant submits herewith a Declaration of Dr. Stanley T. Crooke further supporting the knowledge of one of ordinary skill in the art at the time of filing of the application. Dr. Crooke declares that stabilized oligonucleotides suitable for use in the invention were known and were available to those of ordinary skill in the art in 1981. Dr. Crooke states that, to identify other stabilized oligonucleotides, one of ordinary skill in the art need only begin with the application itself which then points to additional references describing a number of stabilized oligonucleotides available at the time of filing and that such a practice of reviewing additional articles cited in an article of interest to provide background therefor is routine in the art. (Crooke Declaration at 3-6.)

U.S. Patent No. 3,687,808 to Merigan et al. describes stabilized phosphorothioate oligonucleotides available as early as 1972. In addition to the Miller 1977 article, scientific journals published prior to the 1981 filing date of the present application describe a number of stabilized oligonucleotides known in the art. For example, Miller et al. (Biochemistry, 13(24): 4887-4906 (1974) ("Miller 1974")) describe the stabilized alkylphosphotriester DNA analogs described in the application. Matzura and Eckstein (Eur. J. Biochem., 3: 448-452 (1968)) describe the nuclease resistance of phosphorothioate oligonucleotides. Agarwal and Riftina (Nuc. Acids Res., 6:9, 3009-3024 (1979)) describe the synthesis of oligonucleotides containing methyl and phenylphosphonate linkages. DeClercq et al. (Virology, 42:421-428 (1970)) describe the resistance of thiophosphate-substituted oligonucleotides to degradative enzymes. Befort et al. (Chem.-Biol. Interactions, 9:181-185 (1974) ("Befort")) report that ribonucleic acids stabilized by methylation are taken up by cells and exhibit anti-viral activity. Miller et al. (Biochem. 20(7): 1874-1880 (1981) ("Miller 1981")) report a stabilized alkyl phosphonate DNA analog having activity *in vitro*. Holý ("Synthesis and Biological

Activity of Some Analogues of Nucleic Acids Components," in PHOSPHORUS CHEMISTRY DIRECTED TOWARDS BIOLOGY, W.J. Stec, Ed., Pergamon Press, 53-64, 1980) describes modified nucleotide analogs having hydroxyl-containing aliphatic chains that are stable *in vivo* and display inhibitory and substrate activities. Harvey et al. (Biochem. 12(2):208-214 (1973) ("Harvey")) describe 5'-terminal alkyl phosphorothioate groups as protecting groups in oligonucleotide synthesis. Malkievicz et al. (Czech. Chem. Commun., 38:2953-2961 (1973) ("Malkievicz")) demonstrate the use of alkyl thioyl moieties as blocking groups in oligonucleotide synthesis.

That pre-priority date references describing modified oligonucleotides were known to one of ordinary skill in the art prior to Applicant's effective filing date is further evidenced by Summerton et al. (J. Theor. Biol. 78:77-99 (1979) ("Summerton")). The Summerton review of the body of work relating to stabilized oligonucleotides is proof that one of ordinary skill in the art was able to identify other stabilized oligonucleotides at least two years prior to Applicant's effective filing date.

Additionally, the rate of developments in the "field of chemical synthesis" of oligonucleotides in the early 1980s is irrelevant to the present analysis. That improvements to methods of chemically synthesizing oligonucleotides were being made in the early 1980s has no bearing on the patentability of the methods of selectively inhibiting the expression of a target protein in a cell without inhibiting the expression of other proteins.

Moreover, the rate of developments in the field of stabilization of oligonucleotides in the early 1980s was not so rapid, as evidenced by the broad timeframe over which the aforementioned publications became available and as further reflected by references published shortly after the 1981 priority date, that the level of skill in the art changed dramatically over the course of only a few months. For example, Miller et al. (Nucleic Acids: The Vectors of Life, 521-535 (1983) ("Miller 1983")), which was submitted for publication prior to the effective filing date, describe alkyl phosphotriester and methylphosphonate oligonucleotides as nuclease resistant analogs that are taken up by cells in culture. Likewise, Vosberg et al. (J. Biol. Chem., 257(11): 6595-6599 (1982) ("Vosberg")) and Connolly et al. (Biochem., 23(15):3443-3453 (1984)

("Connolly")) describe the nuclease resistance and resulting increased oligonucleotide stability through the use of phosphorothioate linkages.

The conclusion that other forms of stabilized oligonucleotides suitable for *in vivo* use were known in the art in 1981 is buttressed by the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz (initialed and entered by the Examiner as Paper No. 34) and by the declaration of Dr. Crooke submitted herewith (Crooke Declaration at 3-6). The declarants stated that, ***as of the 1981 priority date***, those of ordinary skill were aware of other stabilized forms of oligonucleotides ***suitable for in vivo use*** as taught by the above-identified references (*see, e.g.,* April 14, 1995 declaration of Dr. Ruth at 2-3; Crooke Declaration at 3-6) and that one of skill would have recognized that those stabilized oligonucleotides were useful in the presently claimed methods. The declarants additionally explained that the skilled artisan need only conduct a ***routine*** literature search in the body of knowledge pertaining to stabilized oligonucleotides to locate those sources, there being no other body of knowledge with which one of skill in the art could have been confused. April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz at 4; Crooke Declaration at 3-4. Moreover, such a literature search is routine for one of ordinary skill in the art. Literature searches leading "from the work of one researcher to another" amount to nothing more than the reasonable diligence acceptable under the *Howarth* standard.

3. It is the Examiner's duty to consider the patentability of the claimed invention in view of the record as a whole.

When an applicant submits evidence traversing a rejection, the examiner ***must*** reconsider the patentability of the claimed invention based on consideration of the ***entire record*** with due consideration to the persuasiveness of any arguments. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Applicant asserts that the Examiner has failed to accord proper weight to the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz in view of the record in its entirety.

The Examiner asserts that points 3-5 on page 5 of the response filed July 20, 1995 are mere speculation. Office Action at 11. Applicant disagrees. A declaration is a legal statement based on the knowledge of a skilled artisan, subject to charges of perjury.

Hence, statements made on the basis thereof are necessarily more than mere speculation. Points 3-5 of the July 20, 1995 response are fully supported by the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz and by the Declaration of Dr. Stanley T. Crooke submitted herewith and constitute objective evidence.

Point 3 of the July 20, 1995 response states that "anyone familiar with Miller's work would also have known about Eckstein's work with modified nucleic acids." As explained at page 5 of the April 14, 1995 response, "the alkylphosphotriester DNA analogs described in the application were described in the literature in 1974 by Miller et al. (of record as reference A1). . . . The analog described by Miller in 1981 [of record as reference A2] was an alkyl phosphonate." On that basis, the declarants stated that "[t]he phosphotriester reference in the original application would have lead one of skill directly to Dr. Paul Miller's work . . . . Anyone familiar with Dr. Miller's work would have known of analogous work by Dr. Fritz Eckstein using thio-substituted nucleic acid." This is true because Miller 1974, cited by the Miller 1977 article identified in the application, specifically cites to the work of Eckstein. Point 3 is further supported by the Declaration of Dr. Crooke, wherein the declarant states that "[t]o identify those other stabilized oligonucleotides, one of ordinary skill in the art need only begin with the application itself . . . . [T]he phosphotriester reference in the original application would have 'lead one of skill directly to Dr. Paul Miller's work' and . . . 'anyone familiar with Dr. Miller's work would have known of analogous work by Dr. Fritz Eckstein using thio-substituted nucleic acid.'" Crooke Declaration at 4. Applicant accordingly submits that Point 3 is objective evidence.

Point 4 of the July 20, 1995 response states that "those of skill in science have the ability to conduct literature surveys." Point 5 of the response states that "Dr. Summerton's 1978 (sic) work (A28) expressly summarized the relevant body of knowledge concerning modified oligonucleotides." As declared by both Dr. Ruth and Dr. Schwartz,

> The above references are representative of a significant body of work . . . . For the Examiner to maintain that those of skill would not have known of the above references or not have been able to find the above references is contrary to the way scientists work . . . .

April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz at 4. Additionally, Dr Crooke declares that one of ordinary skill in the art need only conduct a routine literature search to identify other forms of stabilized oligonucleotides suitable for use in the invention. Crooke Declaration at 3. The Summerton reference, which reviews the modified oligonucleotides available in 1979, confirms that a person of ordinary skill in the art would have located the references describing stabilized oligonucleotides with only reasonable diligence as much as two years prior to Applicant's effective filing date. Applicant accordingly submits that Points 4 and 5 of the July 20, 1995 response are objective evidence.

Point 6 of the July 20, 1995 response is dismissed by the Examiner as an opinion. Point 6 states that "two declarants are of the opinion that they would have understood the specification to refer to the various modified nuclease resistant nucleic acid analogs available in 1981." Contrary to the Examiner's position, point 6 is fully supported by the April 14, 1995 declarations of both Dr. Ruth and Dr. Schwartz. Specifically, the declarants stated that "[t]here are several objective reasons why those of skill in 1981 would have understood that the text of the specification . . . was referring to the above identified body of knowledge." April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz at 4. The "above identified body of knowledge" to which the declarants refer includes, for example, Miller 1974 and Befort. Moreover, as established by their credentials, both Dr. Ruth and Dr. Schwartz were skilled artisans as of the 1981 filing date. Accordingly, Applicant submits that Point 6 of the July 20, 1995 response is fully supported by not one but two declarations of persons of skill in the art in 1981 and constitutes objective evidence.

It is clear based on the Examiner's statements (*see, e.g.,* Office Action at 6 (stating that "the declarations by Drs. Schwartz and Ruth (filed April 17, 1995) and the attachments are not convincing")) that he has failed to give due consideration to the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz, the references cited therein, or the arguments based thereon ***in view of the evidence as a whole***. Such consideration is requested by the Applicant.

In short, the issue is whether one type of stabilized oligonucleotide -- phosphotriesters – is sufficient for enablement of the pending claims reciting stabilized oligonucleotides when it is undisputed that other forms of stabilization were known in the art. Among these types are phosphorothioates and alkylphosphonates. It cannot be questioned that this information was available to and known by one of ordinary skill in the art. The fact that forms of stabilized oligonucleotides other than phosphotriesters are not specifically set forth in the specification should be no obstacle to patentability of the solicited claims. Contrary to the Examiner's assertion that the application must specifically mention the different forms of oligodeoxyribonucleotides (Office Action at 7), the application need not teach what is known in the art. A literature search requiring only reasonable diligence to yield the above-identified pre-filing date references and the stabilized forms of oligonucleotides taught therein is reasonably expected of the skilled artisan for enablement purposes. Thus, no undue experimentation in identifying the stabilized oligonucleotides available in 1981 suitable for use in the invention is required.

Accordingly Applicant requests reconsideration and withdrawal of this asserted grounds for rejection.

E. The Application Enables the Use of Oligonucleotides *In Vivo*.

The Examiner has stated that the "applicant's arguments in connection with the existence of any particular form of oligodeoxyribonucleotide at any time prior to the filing of the instant application are most unconvincing in the absence of a mention or teaching in the application as to how to use them." Office Action at 6-7. Having established that one of ordinary skill in the art would know which oligonucleotides to use in the invention, Applicant will now address the alleged failure to teach ***how*** to use the oligonucleotides.

1. The application provides a representative example of how to use oligonucleotides that bears a reasonable correlation to the scope of the claims.

Contrary to the Examiner's implicit assertion that the application must teach how to make and use ***every*** embodiment of the invention, the specification need only disclose

one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims to satisfy the enablement requirement. *In re Fischer*, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970).

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

MPEP § 2164.02.

The specification discloses a phosphotriester oligonucleotide as a representative example of the claimed genus of oligonucleotides that can be used in the invention. The Examiner has stated on the record that the specification is enabling for claims reciting oligodeoxyribonucleotides that are phosphotriesters. *See, e.g.,* Office Action at 2. No more than routine experimentation is required to determine which oligonucleotides work in the invention in view of the examples provided in the application. *See, e.g.,* Substitute Brief at 14 ("[T]he methods for using the different stabilized oligonucleotides are essentially identical to the methods for using the unprotected and the phosphothioester (sic) forms of nucleic acids . . . ."); Specification at 15 ("Testing of the oligonucleotide *in vivo* can be accomplished by adding the oligonucleotide to cultures of cells . . . ."). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Wands*, 8 U.S.P.Q.2d at 1404. As supported by the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz, "nothing beyond routine experimentation was required to administer the antisense oligonucleotides under *in vivo* conditions and detect a downregulation in the expression of a specific protein." April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz at 8. Additionally, Dr Crooke declares that "the methods for using different stabilized oligonucleotides according to the invention are essentially identical to the methods for using phosphotriester oligonucleotides set forth in the application." Crooke Declaration at 6.

It is the Examiner's contention, however, that other members of the claimed genus of oligonucleotides cannot be used in the same manner without undue experimentation to determine which oligonucleotides of the claimed genus will be taken up by cells *in vivo*, will be stable *in vivo*, and will hybridize to the target mRNA *in vivo*. Office Action at 3. Applicant disagrees. The Examiner seems to require that Applicant have performed the testing necessary for FDA approval in order to satisfy the enablement requirement. Applicant refers to MPEP § 2107.03, which states that:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. . . . [I]t is improper for Office personnel to request evidence . . . regarding the degree of effectiveness [in humans] (underlining in original).

Enablement requires only that the specification provide adequate guidance as to how to make and use the invention without undue experimentation. One having ordinary skill in the art would be able to practice this invention having only the application as a guide. Accordingly, the enablement requirement is satisfied. Moreover, although clinical results are not required, the invention has been proven to work time and again by post-filing date references.

2. *The specification provides adequate guidance regarding cellular uptake of oligonucleotides* in vivo.

The Examiner asserts that the application is nonenabling for failure to provide data and methods "for actually getting short DNAs or RNAs into cells." Office Action at 5. The August 19, 1994 declarations of Dr. Ruth and Dr. Schwartz state otherwise, stating that:

> [l]iving cells have a natural capacity for internalizing short nucleic acids. There is nothing to teach. The cells internalize these compounds without special culture conditions. There is no need to render the cells porous. The literature relied upon by the Examiner . . . teaches this fundamental fact. For example, the Miller reference involves the effect of a trinucleotide analog on mammalian cells and the Summerton reference discloses . . . the routine uptake by animal cells of both RNA and DNA. Finally there is the paper by Zamecnik and Stephenson (1978) which

> describes the internalization of viral infected cells by a DNA of 13 nucleotides.

August 19, 1994 declarations of Dr. Ruth and Dr. Schwartz at 4. As supported by the Declaration of Dr. Crooke (page 6), it was known in the art in 1981 that oligonucleotides, stabilized and unstabilized, are taken up by cells. For example, several references cited by Applicant as support for the knowledge of other forms of stabilized oligonucleotides in 1981 report that their stabilized oligonucleotides are internalized by cells. Substitute Brief at 17. For example, the Befort article reports that "[a]ll RNAs, modified or not, enter the cells . . . ." Befort at 181. *See also* Miller 1981 abstract ("Tritium-labeled oligodeoxyribonucleoside methylphosphonates . . . are taken up intact by mammalian cells in culture."); and Summerton at 84 (describing the uptake of DNA and RNA by prokaryotic and eukaryotic systems).

The Examiner contends that the declarations, brief, and references relied upon therein are not convincing because they "do not address the issue of stability in vivo." Office Action at 6. A showing of *in vivo* stability, however, is not required for enablement. The Examiner is reminded that enablement requires only that the application teach how to make and use the invention without undue experimentation. The application satisfies this requirement by providing *in vitro* models of cellular uptake of the oligonucleotides of the invention. Moreover, the *in vitro* models presented in the pre-1981 publications are recognized in the art as reasonably correlating to *in vivo* conditions. A rigorous or exact correlation is not required, as stated in *Cross v. Iizuka*:

> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed in vitro utility and in vivo activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). The initial burden is on the Examiner to give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. MPEP §2164.02. The Examiner has failed to meet this burden.

The Examiner cites Gura and Rojanasakul as evidence that cells will not internalize stabilized oligonucleotides *in vivo*. As declared by Dr. Crooke,

> Moreover, I note that Gura is not a peer-reviewed article by a practicing scientist. Rather the article was written by a ***reporter*** **for the *Chicago Tribune***. Gura at 577. Gura merely represents a biased and untrained assessment of antisense technology by an individual having no skill in the art who solicited the ***opinions of admitted skeptics*** of the technology, including Cy Stein, Arthur Krieg, and others. Gura at 575. The news article contains no counterbalancing opinions by those who have been successful in oligonucleotide technology. The lengthy prosecution of the present application has allowed us to witness the successes achieved in the field of antisense technology, ratifying the views of proponents of antisense at the time of the invention and silencing, and indeed converting, many critics to what is clearly the correct view. ***Scientifically grounded, peer-reviewed journal articles*** support the fact that stabilized oligonucleotides are internalized by cells. These journal articles were authored by individuals of ordinary skill practicing nothing more than what is taught by the present application. In sum, Tullis was right then – true scientists knew it – and is right today.

Crooke Declaration at 7.

Moreover, even Gura proves that antisense molecules do enter cells. Gura summarizes several *in vivo* studies of the biological effects of stabilized oligonucleotides. Gura does ***not*** report that no stabilized oligonucleotides enter ***cells*** *in vivo*, but rather that researchers have encountered difficulties in getting antisense drugs into target ***tissues*** *in vivo*. In fact, the *in vivo* studies summarized by Gura report accumulation of phosphorothioates in the kidneys, liver, and bone marrow of test animals, thus supporting cellular internalization of the oligonucleotides. Gura at 576. Furthermore, that modified oligonucleotides may "get hung up on proteins outside cells" does ***not*** suggest that the oligonucleotides do not enter cells at all. *Id.* In other words, that all of the oligonucleotides may not be internalized by cells *in vivo* does not support a finding of nonenablement. Enablement does not require 100% success. In *Wands*, the claims were found to be enabling even though only 4 out of 143 (only 2.8%) hybridomas producing monoclonal antibodies were successful. 8 U.S.P.Q.2d at 1406. Thus, Applicant submits that Gura actually supports the internalization of stabilized oligonucleotides by cells *in vivo*.

Rojanasakul reports that stabilized oligonucleotides are "poorly taken up by cells[:]" "When added directly to cells in culture, only 1-2% of the added

[oligonucleotides] become cell-associated." Rojanasakul at 118, 120. Under *Wands*, however, that "1-2% of the added [oligonucleotides] become cell-associated" weighs in favor of enablement of the solicited claims. Rojanasakul also reports that there are "examples of successful in vivo treatment in the absence of specialized delivery systems." *Id.* at 118. Additionally, Rojanasakul reports that phosphorothioate oligonucleotides readily compete with unmodified oligonucleotides for cellular uptake and that methylphosphonates also enter cells. *Id.* at 120. These findings do not support a conclusion of lack of enablement for failure to establish cellular uptake. In fact, Rojanasakul specifically demonstrates cellular uptake of the oligonucleotides. The Examiner is again reminded that enablement does not require 100% success under *Wands*. Only some effect is necessary to satisfy the enablement requirement. Thus, Applicant asserts that Rojanasakul supports a finding of enablement.

Moreover, Applicant has properly submitted several post-filing date references supporting the *in vivo* cellular uptake of modified oligonucleotides. In *Gould v. Quigg*, the Federal Circuit confirmed that "a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling" but held that it was not error to consider a later dated publication as evidence of "the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative." 3 U.S.P.Q.2d 1302, 1305 (Fed. Cir. 1987). Applicant asserts that the present disclosure was sufficient and that the post-filing date references lend additional support to Applicant's arguments establishing enablement of the claims as set forth in the lengthy prosecution of the present application. If the Examiner disagrees with this standard for consideration of later-dated references, Applicant requests that the Examiner cite to the relevant evidence upon which he relies. 37 C.F.R. § 1.104(d)(2).

Phillips et al. (Kidney International, 46: 1554-1556 (1994)) report the *in vivo* effects of phosphorothioated oligodeoxynucleotides simply injected into the brains of rats and concluded that "[o]ur present results do show that sufficient [oligodeoxynucleotide] uptake occurs in vivo to provide inhibition of blood pressure which appears to be related to the inhibition of angiotensin gene or AT_1 receptor gene expression." Phillips at 1556. Additionally, Hijiya et al. (Proc. Natl. Acad. Sci. 91: 4499-4503 (1994)) report that phosphorothioate-modified antisense oligodeoxynucleotides targeted to the MYB

protooncogene controlled the growth of a human leukemia in a SCID mouse model. Thus, Phillips and Hijiya establish the operability of the claimed methods. Mercola et al. (Cancer Gene Therapy, 2(1): 47-59 (1995)) lend further support to the *in vivo* operability of stabilized oligonucleotides, describing several studies in which phosphorothioate oligonucleotides administered systemically downregulate the *in vivo* expression of their target oligonucleotides. *See, e.g.,* Mercola at 54-55. Additionally, Putnam (Am. J. Health-Syst. Pharm. 53: 151-160 (1996)) describes several *in vivo* studies demonstrating cellular uptake of modified oligonucleotides. *See, e.g.,* Putnam at 154 ("When day-old Pekin ducklings were infected with duck hepatitis B virus and then, two weeks later, given daily intravenous injections of an antisense oligonucleotide for 10 days, there was reproducible dose-dependent inhibition of viral replication."); 156 ("In vivo studies in rats have also yielded promising results. Antisense oligonucleotides recognizing *c-myc*, cdk 2, and cdc 2 inhibited the proliferation of smooth muscle cells after carotid artery angioplasty.") (citations omitted). These post-filing date references confirm what was already known regarding cellular uptake of stabilized oligonucleotides in October 1981.

Given that the Examiner has provided no evidence to suggest that the *in vitro* models described in the August 19, 1994 declarations of Dr. Ruth and Dr. Schwartz, the Substitute Brief, and the Crooke Declaration are not predictive of the cellular uptake of the stabilized oligonucleotides *in vivo* on the basis of the teachings of Gura and Rojanasakul, Applicant submits that the Examiner has not established a *prima facie* case of nonenablement. Moreover, Gura, Rojanasakul, and the cited post-filing date references support a finding of enablement. Applicant accordingly requests reconsideration and withdrawal of this basis for rejection.

3. *The specification provides adequate guidance regarding the* in vivo *stability of oligonucleotides.*

The specification teaches that both unstabilized and stabilized oligonucleotides will work in the invention. As previously explained, an unprotected oligonucleotide would work in the invention: it would enter the cell, bind to the target mRNA, and inhibit expression of the target protein encoded thereby. Applicant recognizes that an unprotected oligonucleotide would likely not achieve the ***level*** of inhibition of expression

of the target protein achieved by a stabilized oligonucleotide, as a result of more rapid degradation. This, however, does not suggest that an unprotected oligonucleotide will not work in the invention.

The specification further teaches that the oligonucleotides used in the methods of the invention may be stabilized, such as transformed to a phosphotriester form, to enhance resistance thereof to degradative enzymes. *See, e.g.,* Specification at 4, 18. The declarations of Dr. Ruth and Dr. Schwartz filed on April 14, 1995 and the Appeal Brief (pages 6-21) also address the issue of stability of the modified oligonucleotides known in the art in October 1981. It was known by those of ordinary skill in the art in 1981 that modified oligonucleotides are stable in cells. For example, as previously noted, several of the references cited in the April 14, 1995 declarations support the contention that stabilized oligonucleotides were known in the art at the time of filing of the parent application and clearly demonstrate the stability of the stabilized oligonucleotides discussed therein. *See, e.g.,* Befort at 181 (reporting inhibition of Sindbis virus by chemically modified RNAs in chicken embryo fibroblasts).

Despite this teaching, the Examiner alleges that the application is nonenabling for claims reciting methods using stabilized oligonucleotides other than phosphotriesters based on an alleged failure of the application to establish the *in vivo* stability of the stabilized oligonucleotides. Enablement, however, does not require such a teaching. Enablement requires only that the application teach how to make and use the invention without undue experimentation. The application demonstrates the use of stabilized oligonucleotides *in vitro* and teaches their use *in vivo.* This is all that is required for enablement.

The Examiner first relies on the file history of U.S. Patent No. 5,919,619 (the '619 patent) to rebut the correlation between the *in vitro* evidence and *in vivo* stability. The Examiner states that "[t]he prosecution history of the '619 patent shows that the application enables the practice of inhibition of expression only in cells in culture and only using stabilized oligonucleotides. . . ." Office Action at 4. Applicant traverses.

Nowhere in the '619 patent file history is it even suggested that the application enables the practice of inhibition of expression of the target protein ***only*** in cells in culture; rather, the '619 file history demonstrates that the application is enabling ***at least***

with respect to inhibition of expression in cell culture. Additionally, the Examiner's assertion that the application enables only stabilized oligonucleotides is not supported by the '619 file history; instead, the '619 file history demonstrates that the Rojanasakul reference relied upon by the Examiner confirms that unmodified oligonucleotides bind to mRNAs and inhibit expression in cell culture. *See, e.g.,* '619 Response filed May 9, 1992 at 7. Furthermore, there is no statement in the '619 file history to the effect that "the issue of breakdown of the oligonucleotides in body tissues was not a factor in cell culture environment;" rather, the file history explains that breakdown of oligonucleotides can be overcome by increasing the concentration of the oligonucleotide, which is "more easily undertaken when using cell cultures." *See, e.g.,* '619 Response filed May 9, 1992 at 8. Again, this is a question of degree of success, not whether or not success is achieved at all.

The Examiner further alleges that the declarations by Drs. Ruth and Schwartz (filed September 6, 1994) and pages 6-21 of the brief "are not convincing because these arguments and declarations do not address the issue of stability of the oligodeoxyribonucleotides in vivo (the declarations are silent on this issue)." Office Action at 6. The Examiner points to Gura and Rojanasakul as support for the alleged difficulties regarding the *in vivo* stability of modified oligonucleotides. *See id.* at 3.

As declared by Dr. Crooke,

> Gura . . . poses the incorrect question. The appropriate question that should have been posed in that news article is not "do antisense compounds 'work the way researchers once thought they did'?" but rather "what are the pharmacokinetic data regarding the stability of modified oligonucleotides in cells and in an integrated system, such as an animal?" As presented herein, ***scientifically grounded, peer-reviewed journal articles*** support the fact that modified oligonucleotides are stable in cells. These journal articles were authored by individuals of ordinary skill practicing nothing more than what is taught by the present application.

Crooke Declaration at 8-9.

Moreover, contrary to the Examiner's assertion, even Gura ***supports*** the stability of modified oligonucleotides *in vivo* by describing the effects resulting from administration thereof in cell culture and *in vivo*. *See, e.g.,* Gura at 575 ("Researchers

also made [the oligonucleotides] more resistant to the many enzymes that break down nucleic acids by replacing a critical oxygen atom in each nucleotide building block with a sulfur atom."); 577 (describing the *in vivo* effects of phosphorothioate oligonucleotides). Likewise, Rojanasakul supports the *in vivo* stability of modified oligonucleotides. *See, e.g.,* Rojanasakul abstract (explaining that protected or modified oligonucleotides are stabilized against degradation in a biological environment); 119 (describing chemically modified oligonucleotides, including phosphorothioates, phosphorodithioates, and methylphosphonates, as preferred alternatives to naturally occurring phosphodiester oligonucleotides in view of *in vivo* stability). It is axiomatic that for an oligonucleotide to be exhibit activity *in vivo*, it ***must*** be stable *in vivo* for a certain amount of time.

Moreover, several references published after the earliest effective filing date of the application reinforce the operability of oligonucleotides *in vivo*, and hence their stability *in vivo*. For example, Phillips et al. (Kidney International 46: 1554-1556 (1994)) report that injections of phosphorothioated antisense oligodeoxynucleotides directed against angiotensin II type 1 mRNA into hypertensive rats produced a long lasting decrease in blood pressure. Additionally, Hijiya et al. (Proc. Natl. Acad. Sci. 91:4499-4503 (1994)) demonstrate that subcutaneous administration of phosphorothioated oligonucleotides targeting the MYB protooncogene suppressed MYB gene expression in a SCID mouse model. Mercola and Cohen (Cancer Gene Therapy 2(1): 47-59 (1995)) describe studies in which systemic delivery of modified oligonucleotides yields significant downregulation of expression of the targeted gene *in vivo*. Similarly, Putnam (Am. J. Health-Syst. Pharm. 53:151-160 (1996)) summarizes several studies in which modified oligonucleotides exhibit inhibitory effects *in vivo*.

Given that the Examiner has proffered no evidence to suggest that the *in vitro* models described in the April 14, 1995 declarations of Dr. Ruth and Dr. Schwartz, in the Substitute Brief, and in the Crooke Declaration are not predictive of the stability of the stabilized oligonucleotides *in vivo* on the basis of the teachings of Gura and Rojanasakul, Applicant submits that the Examiner has failed to establish a *prima facie* case of nonenablement. Moreover, Gura, Rojanasakul, and the other cited post-filing date references support a finding of enablement. Applicant accordingly requests reconsideration and withdrawal of this basis for rejection.

4. The specification provides adequate guidance regarding the specificity of in vivo *hybridization of the stabilized oligonucleotides.*

The Examiner cites the alleged failure to establish the specificity of hybridization of stabilized oligonucleotides as another basis for the enablement rejection. *See, e.g.,* Office Action at 3. Enablement, however, does not require such a teaching. Enablement requires only that the application teach how to make and use the invention without undue experimentation. The application demonstrates the use of stabilized oligonucleotides *in vitro* and teaches their use *in vivo.* This is all that is required for enablement. As explained in the application at page 11:

> [i]n order to obtain a high degree of specificity, an oligomer of about fourteen or more residues can be constructed. Although shorter sequences will work, longer sequences will provide higher specificity. This can readily be seen mathematically. Whereas a ten unit polymer chosen from four bases can have 4^{10} (1,048,576) ramdom (sic) combinations, a 20-unit polymer has 4^{20} random combinations, which equals 1.09×10^{12} (1,090,000,000,000).

Example 1, as a representative example of stabilized oligonucleotides, demonstrates that specificity of hybridization is ***not*** reduced by modification of the oligonucleotide.

The amendment submitted July 20, 1995 explains that the application provides guidance regarding the *in vivo* specificity of hybridization of stabilized oligonucleotides, including RNA and DNA analogs. Given the representative example of a stabilized oligonucleotide in the application, no undue experimentation would be required to determine which other forms of oligonucleotides, including stabilized oligonucleotides, demonstrate specific hybridization using the application as a guide. Moreover, it was known in the art in 1981 that stabilized oligonucleotides bind specifically to their targets in cell culture. For example, Miller 1981 teaches that phosphonate analogs specifically bind intracellularly to initiation sites and tRNA binding sites of mRNA. Additionally, Befort uses artificially methylated nucleic acids to inhibit viral replication in cell culture. The Summerton reference also states that analogs and derivatives of nucleic acids function as a result of specific base pairing:

> [T]here are a growing number of reports on antiviral and/or anticancer activity of homopolyribonucleotides, analogs, and derivatives thereof, and a synthetic oligodeoxy-ribonucleotide. The general rationale for this work is that the introduction of such polymers into virally infected cells may lead to pairing between the introduced polymer and a specific viral structure of nucleotide sequence. Presumably such pairing would inhibit some critical function in the virus life cycle.

Summerton at 89. Thus, in stark contrast to the Examiner's contention that only single stranded oligonucleotides would work in the invention, double-stranded oligonucleotides are available for use in the claimed methods.

The Examiner asserts that Applicant's arguments that the application provides guidance regarding the specificity of *in vivo* hybridization of the stabilized oligonucleotides are unconvincing. The Examiner relies on Gura and Rojanasakul as allegedly indicating that "hybridization characteristics of stabilized forms of nucleic acids differ from those of non-modified forms and that non-specific effects are seen in cells treated with oligonucleotides." Office Action at 13.

As stated by Dr. Crooke in the declaration submitted herewith,

> Gura . . . poses the incorrect question. The appropriate question to be answered is "what are the specificity indices of stabilized oligonucleotides in cells and in an integrated system, such as an animal?" In fact, as presented herein, ***scientifically grounded, peer-reviewed journal articles*** support the fact that stabilized oligonucleotides hybridize specifically. These journal articles were authored by individuals of ordinary skill practicing nothing more than what is taught by the present application.

Crooke Declaration at 10.

Gura actually reports that control oligonucleotides elicited similar results as test oligonucleotides in cell culture. Gura at 576. Gura also reports, however, that this effect is ***not*** necessarily exclusive to an antisense effect. *See id.* at 577 (in which Columbia University professor Cy Stein suggests that antisense drugs are likely to "work by many mechanisms, of which antisense is one"). Similarly, Rojanasakul reports that several studies "appear to suggest that cellular toxicity and non-specific activity of antisense oligonucleotides can occur (albeit in cell culture systems)." Rojanasakul at 118. Rojanasakul also reports, however, that "the in vitro effects of [oligonucleotides] may not

necessarily reflect their in vivo effects, and there are studies which indicate the relative safety of antisense [oligonucleotides] in vivo." *Id.*

Moreover, Phillips and Hijiya demonstrate the operability of the claimed methods of the invention. Not only did the modified oligonucleotides of Phillips and Hijiya enter cells, as previously established, but they exhibited downregulation of expression of their target proteins. Mercola et al. (Cancer Gene Therapy, 2(1): 47-59 (1995)) and Putnam (Am. J. Health-Syst. Pharm., 53: 151-160 (1996)) lend further support to the *in vivo* operability of stabilized oligonucleotides. Mercola describes several studies in which phosphorothioate oligonucleotides downregulate the *in vivo* expression of their target oligonucleotides. *See, e.g.,* Mercola at 54-55. Likewise, Putnam states that "[m]odification of the phosphodiester linkages in oligonucleotides can lend the sequences enzymatic stability without affecting their binding capacities." Putnam, abstract. The modifications referred to in Putnam include phosphorothioates, methylphosphonates, methylphosphotriesters, ethylphosphotriesters, and alkylphosphoramides. Putnam at 157, Figure 3.

Given that the Examiner has provided no evidence to suggest that the *in vitro* models described in the July 20, 1995 response are not predictive of the specificity of hybridization of the stabilized oligonucleotides *in vivo* on the basis of the teachings of Gura and Rojanasakul, Applicant submits that the Examiner has not established a *prima facie* case of nonenablement. Moreover, the cited post-filing date references confirm the operability of the claimed invention. Applicant accordingly requests reconsideration and withdrawal of this basis for rejection.

In view of the foregoing, Applicant submits that enablement requires only that the specification provide adequate guidance as to how to make and use the invention without undue experimentation. This requirement has been met. At the time of filing, one of ordinary skill in the art would have been able to make and use the claimed invention using the application as a guide. Consideration of the *Wands* factors weighs in favor of a finding of enablement: (1) the breadth of the solicited claims reasonably correlates to the enabled examples using phosphotriester oligonucleotides; (2) numerous modified oligonucleotides were known to one of skill in the art at the time of filing; (3) one of skill

in the art of molecular biology in 1981 was highly sophisticated; (4) the specification as filed provided ample guidance, including examples, to one of skill in the art at the time of filing as to how to make and use the invention, which is all that is required for enablement; and (5) nothing more than routine experimentation was required to determine which modified oligonucleotides are most effective in the methods of the invention.

Applicant has established herein that: (1) as of the priority date, one of skill in the art was aware of the existence of stabilized forms of oligonucleotides other than phosphotriesters and was guided by the disclosure of the application to the other stabilized oligonucleotides that are equally suitable as phosphotriester oligonucleotides for *in vivo* use according to the claimed invention; (2) nothing more than routine experimentation using the application as a guide is involved in determining which forms of stabilized oligonucleotides will work in the invention; (3) the stabilized oligonucleotides known in the art at the effective filing date are taken up by cells, are sufficiently stable to exert biological activity, and specifically hybridize; and (4) *in vitro* models correlate to *in vivo* biological activity of the stabilized oligonucleotides.

Applicant submits that the evidence, when considered as a whole, establishes enablement of the solicited claims. Accordingly Applicant requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112.

CONCLUSION

Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a notice of allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-568-3100.

Attached hereto is a marked-up version showing changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Date: June 17, 2002

Respectfully submitted,

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Enclosures
- Declaration of Dr. Stanley T. Crooke
- Supplemental Information Disclosure Statement
- Form PTO-1449
- Copies of References Cited

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

All of the claims presently pending are set forth below:

64. A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

(a) synthesizing an oligonucleotide having a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid said subsequence coding for the target protein,

(b) introducing the oligonucleotide into the cell; and,

(c) hybridizing the oligonucleotide to the subsequence of the messenger ribonucleic acid to inhibit the expression of the target protein.

Please amend claims **65-72** to read as follows:

65. **(Amended)** [A] The method of claim 64 wherein the entire sequence of the oligonucleotide is complementary to the subsequence of a messenger ribonucleic acid coding for the target protein.

66. **(Amended)** [A] The method of claim 64 wherein the oligonucleotide is at least 14 bases in length.

67. **(Amended)** [A] The method of claim 64 wherein the oligonucleotide is about 23 bases in length.

68. **(Amended)** [A] The method of claim 64 wherein the oligonucleotide is between 14 and 23 bases in length.

69. **(Amended)** [A] The method of claim 64 wherein the messenger ribonucleic acid is viral.

70. **(Amended)** [A] The method of claim 64 wherein the messenger ribonucleic acid encodes a hormone.

71. **(Amended)** [A] The method of claim 64 wherein the oligonucleotide is stabilized to inhibit degradation by nucleases.

72. **(Amended)** [A] The method of claim 64 wherein the oligonucleotide is [a] an oligodeoxynucleotide.

Please add the following new claims **73-83:**

73. **(New)** A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

selecting a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes and has a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of said cell, said subsequence coding for the target protein,

introducing said synthetic oligonucleotide into the cell, and

hybridizing said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid to inhibit the expression of the target protein.

74. **(New)** The method of claim 73 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.

75. **(New)** A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other

proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

selecting a synthetic oligonucleotide that has enhanced resistance against nuclease enzymes and has a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid of said cell, said subsequence coding for the target protein, and

introducing said synthetic oligonucleotide into the cell at a temperature between 0°C and 80°C to hybridize said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid.

76. **(New)** The method of claim 75 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.

77. **(New)** The method of claim 75 wherein said temperature is between 10°C and 40°C.

78. **(New)** A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acid encoding the target protein, said method comprising the steps of:

selecting a base sequence substantially complementary to said messenger ribonucleic acid of said cell coding for the target protein,

providing a synthetic oligonucleotide that is stabilized against *in vivo* degradative enzymes, said synthetic oligonucleotide having said selected base sequence, and

introducing said synthetic oligonucleotide into the cell whereby said synthetic stabilized oligonucleotide hybridizes to the subsequence of the messenger ribonucleic acid.

79. **(New)** The method of claim 78 wherein said synthetic oligonucleotide is between 14 and about 23 bases in length.

80. **(New)** A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein, said method comprising the steps of:

selecting a plurality of base sequences that are complementary to said messenger ribonucleic acid,

providing a synthetic oligonucleotide corresponding to each of said base sequences,

selecting a preferred one of said synthetic oligonucleotides for inhibition of the expression of said target protein in a cell, and

using said selected oligonucleotide for inhibition of said target protein in cells.

81. **(New)** The method of claim 80 wherein said synthetic oligonucleotides are oligonucleotides stabilized against *in vivo* degradative enzymes.

82. **(New)** The method of claim 80 wherein said selected synthetic oligonucleotide is between 14 and about 23 bases in length.

83. **(New)** The method of claim 80 further comprising the step of synthesizing bulk amounts of said selected oligonucleotide for inhibition of said target protein *in vivo*.